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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/525,673 | 04/18/2005 | Martin W. Brechbiel | 232522 | 9574 |

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| EXAMINER | |
|---|---|
| MURRAY, JEFFREY H | |
| ART UNIT | PAPER NUMBER |
| 1609 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 06/06/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/525,673 | BRECHBIEL ET AL. | |
| | Examiner | Art Unit | |
| | Jeffrey H. Murray | 1609 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *24 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,6,8 and 11-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,8 and 11-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *24 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/24/2005, 3/22/2005, and 8/30/2006.

## DETAILED ACTION

1. There are thirty-three claims pending and twenty-seven under consideration. Claims 2,4-5,7, and 9-10 have been cancelled. This is the first action on the merits. The application concerns some backbone-substituted macrocyclic chelates, in particular the substituted macrocyclic chelating agent, 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid ("DOTA"), metal complexes thereof, and methods of using same.

### *Priority*

2. Acknowledgment is made of Applicant's claim for domestic priority. This current application, 10/525,673, filed February 24, 2005, is a national stage entry of PCT/US03/27878, filed September 5, 2003, which claims the benefit of provisional priority to 60/408,676, filed September 6, 2002.

### *Specification*

3. The disclosure is objected to because of the following informalities:

On page 33 of the specification, Table 3, footnote a, the trademark HERCEPTIN is missing its trademark symbol (™). Appropriate correction is required.

4. The use of the trademark HERCEPTIN has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any of the errors of which applicant may become aware of in the specification.

### *Claim Objections*

6. Claim 17 is objected to because of the following informalities:

Claim 17 refers to a metal ion, therefore the metal, Gd, should be written in ionic form to be consistent with the rest of the application. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3, 6, 8, and 11-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for formula I and II of Claim 1, does not reasonably provide enablement for formula III of Claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (United States v. Teletronics Inc., 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a

conclusion reached by weighing many factors (See Ex parte Forman 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

These factors include the following:

1) *Amount of guidance provided by Applicant.* While the Applicant has demonstrated within the application how to make and use the compounds and compositions of formula I and II, they have failed to demonstrate within the application how to make and use the compounds and compositions of formula III. In the specification, page 17-26 describes the experimental procedures for making various derivatives of formula I and II. The specification makes no attempt to show a synthesis of formula III. The same holds true for the compound in Claim 3, which is merely a particular stereoisomer of the compound of formula III.

2) *Number of working examples.* Applicant has provided working example compounds of formulas I and II. No working examples have been provided for formula III in the present application.

3) *Scope of the claims.* The scope of the claims involve all of the compounds and compositions of general formula I, II, and III. It also involves all of the potential uses of these compounds and compositions such as metal complexes, use for diagnostic imaging of a host, use for magnetic resonance imaging of a host, use for X-ray imaging of a host, and the use for treating a cellular disorder. Thus, the scope of claims is very broad.

4) *Nature of the invention.* The nature of this invention relates generally to backbone-substituted macrocyclic chelates, in particular the substituted macrocyclic chelating agent, 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid ("DOTA"), metal complexes thereof, and methods of using same.

5) *Level of skill in the art.* The artisan using Applicants invention would be a physician with a M.D. degree, and having several years of experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions or treating the diseases mentioned.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 15-16, 18, 20, 22, and 29-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 17 recites the limitation "...the complex comprises Gd." Claim 17 refers back to claim 16, which recites a metal ion. Gd stands for the rare earth element Gadolinium. As there are numerous isotopes and therefore multiple ions available to Gadolinium, applicant should point out distinctly the ion or ions of Gadolinium they wish to cite as their invention. Appropriate correction is required.

### *Claim Rejections - 35 USC § 103*

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

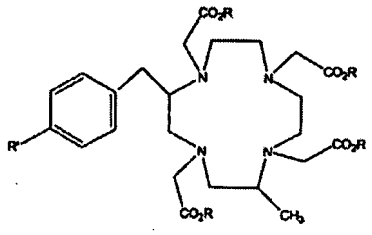
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

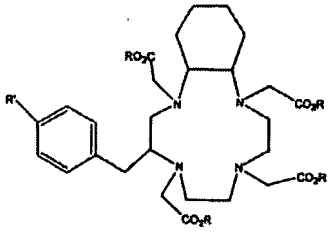
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 1, 6, 11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moi et. al. in view of US 5,049,667. ('667)

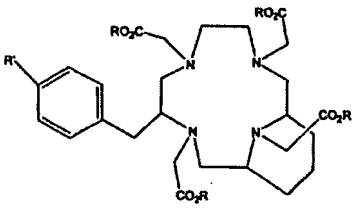
The current application recites a variety of backbone-substituted macrocyclic chelates, in particular the substituted macrocyclic chelating agent, 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid ("DOTA"), metal complexes thereof, and methods of using them. In this application there is the presence of three particular formulas, I-III exist:



I



II



III

Moi et. al. recites the synthesis of p-nitrobenzyl-DOTA. (p.6266, Fig.1, **1**) This is the same structure as formula I above, where R is a hydrogen and R' is a nitro group, only lacking the methyl substitutent.

'667 recites the synthesis of 2-methyl DOTA, or MDOTA. (Col.18, Example 6) This is also the same structure as formula I above, where R is a hydrogen, only lacking the p-nitrobenzyl substitutent.

Both references cite the same use for their respective compounds. Moi et. al states, "DOTA is a stable useful contrast agent for *magnetic imaging*." (emphasis added). Moi et. al. even cites applicant's own work to show this fact. '667 discusses its present invention and states, "The present invention relates to new nitrogen-containing cyclic ligands and metallic complexes formed by these ligands, the uses of these complexes as *magnetic resonance imaging agents, as X-ray contrast agents and as chemical shift reagents in vivo*." (emphasis added).

It would have been obvious to one skilled in the arts at the time of the invention to be motivated to combine references and synthesize a DOTA derivative containing both the p-nitrobenzyl group and the methyl group to form a compound or composition of formula I. Moi et. al. combined with '667 show the necessary teachings that suggest combining the substituents of the two structures to form a DOTA moiety containing both the p-nitrobenzyl and the methyl group in an attempt to enhance activity and afford a positive benefit from the replacement.

15. Claims 1, 3, 6, 8, and 11-19, and 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moi et. al. in view of US 5,358,704. ('704)

'704 recites the synthesis of 2,3-cyclohexyl DOTA. This is also the same structure as formula II above, where R is a hydrogen, only lacking the p-nitrobenzyl substitutent.

Both references cite the same use for their respective compounds. '704 discusses its present invention and states, "These compounds are useful, for example, as metal-chelating ligands and, in the form of metal complexes, the present compounds are especially useful as diagnostic contrast agents. When the metal in the complex is paramagnetic, the diagnostic contrast agents are suitable for magnetic resonance imaging, and are *particularly useful for magnetic resonance imaging (MRI)* of the liver and bile ducts." (emphasis added).

It would have been obvious to one skilled in the arts at the time of the invention to be motivated to combine references and synthesize a DOTA derivative containing both the p-nitro benzyl group and the cyclohexyl group to form a compound or composition of formula II. Moi et. al. combined with '667 show the necessary teachings that suggest combining the 2 structures to synthesize a DOTA moiety containing both a p-nitrobenzyl group and a cyclohexyl group to attempt to enhance activity and afford a positive benefit from the replacement.

16. Claims 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moi et. al., '667, and '704 in view of US 5,428,156. ('156)

Moi et. al., '667, and '704 recited earlier as a combination the obvious reasons to synthesize the compounds or compositions of formula I and II in Claims 1 and 3. What they lack is a reason to use these compounds or compositions for SPECT imaging.

'156 discusses its present invention and shows the same compound of Moi et. al., i.e. a p-nitrobenzyl DOTA molecule. '156 states,

> "The chelates of the invention may also be used in Emission Tomography to measure physiological function of organs and related biochemical processes in both health and disease. The two modes of emission tomography are single-photon emission computed tomography (SPECT) and positron emission tomography (PET). SPECT uses radionuclides that emit a single photon of a

> given energy and these include gamma ray emitters such as $^{67}Ga$, $^{97}Ru$, $^{99m}Tc$, $^{111}In$, $^{123}I$, $^{131}I$, $^{203}Pb$, and others. PET uses radionuclides known as positron emitters such as $^{11}C$, $^{15}O$, $^{18}F$, $^{55}Co$, $^{78}Cu$, $^{68}Ga$, $^{75}Br$, $^{89}Zr$, $^{124}I$, and others for coincidence detection in which the positron and electron annihilate each other to form two photons at 180 degrees."

It would have been obvious to one skilled in the arts at the time of the invention to be motivated to combine references and use a DOTA derivative containing both the p-nitrobenzyl group and the methyl or cyclohexyl group for SPECT imaging. Moi et. al., '667, and '704 combined with '156 show the necessary teachings that suggest combining the obvious DOTA structures to be used for SPECT imaging in an attempt to enhance activity and afford a positive benefit from the replacement.

17. Claims 22-27, and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moi et. al., '667, and '704 in view of US 5,428,154. ('154)

Moi et. al., '667, and '704 recited earlier as a combination the obvious reasons to synthesize the compounds or compositions of formula I and II in Claims 1 and 3. What they lack is a reason to use these compounds or compositions for treating a cellular disorder such as cancer or to form a conjugate with a biomolecule.

'154 discusses its present invention and shows the same compound of Moi et. al., i.e. a p-nitrobenzyl DOTA molecule. '154 states,

> "A macrocycle of particular usefulness as a chelate is the 1,4,7,10-Tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA). *DOTA compounds have been linked to biomolecules to form delivery systems for the chelated metal ion to specific sites within an organism...The invention includes a process for treating cellular disorders.* This process uses the chelate conjugate with a hapten having a selective binding site at the cellular disorder. For example, Q can be a monoclonal antibody, wherein the antibody is directed and created against an epitope found specifically on the tumor cells. Thus, when $Pb^{212}$ is transported to the antegen site and, subsequently, decays in secular equilibrium to $Bi^{212}$ and its daughters, a beta irradiation is produced from the

> lead disintegration. A beta radiation is produced by the bismuth daughters. This beta radiation is similar to the beta radiation from $Y^{90}$ but, in addition each disintegration of bismuth also produces an alpha particle. In this manner, a radiotherapy is provided with a radiation dose from both an alpha and a beta particle. If desired, only $Bi^{212}$ can be introduced in those cases where the disorder to be treated, such as with leukemic cells, can be easily reached within the 1 hour half-life of $Bi^{212}$. *It is also possible to use this method to treat cancers,* where the cells are widely differentiated." (emphasis added).

It would have been obvious to one skilled in the arts at the time of the invention to be motivated to combine references and use a DOTA derivative containing both the p-nitrobenzyl group and the methyl or cyclohexyl group for treating a cellular disorder such as cancer or to form a conjugate with a biomolecule. Moi et. al., '667, and '704 combined with '154 show the necessary teachings that suggest combining the obvious DOTA structures to be used in treating a cellular disorder such as cancer or to form a conjugate with a biomolecule in an attempt to enhance activity and afford a positive benefit from the replacement.

***Conclusion***

18. Claims 1, 3, 6, 8, and 11-33 are rejected.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on M-F 7:30-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Cecilia Tsang can be reached at 571-272-0562 or Janet Andres can be reached at 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jeffrey H. Murray

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER